REMARKS

Status of the Claims

Claims 1-37 were rejected. Claim 31 has been canceled without prejudice or disclaimer. Claims 1-30 and 32-37 remain pending.

Claims 1, 15, 16, 18, 31-35 and 37 have been amended. Specifically, claims 1 and 16 have been amended to remove the limitation which recites conserved amino acid sequences in SEQ ID NO:40. Claim 15 has been amended to be independent. Claims 32-35 and 37 have been amended to change dependency, and claim 18 has been amended to correct an obvious typographical error. No new matter has been added by way of these amendments.

Amendments to the Specification

Per the Examiner's request, the incomplete citation appearing on page 21 has been removed. In addition, proper sequence identifiers have been added to page 57. No new matter has been added by way of these amendments.

Amendments to the Sequence Listing

A substitute sequence listing is submitted herewith. SEQ ID NO:40 in the substitute sequence listing has been amended. The sequence set forth in SEQ ID NO:40 comprises the consensus sequence found in Figure 2. The original sequence listing lacked the variant/deleted amino acids which are represented in the consensus sequence of Figure 2 as "---". The amended SEQ ID NO:40 now contains "Xaa" at these positions and thus, correctly reflects the sequence appearing in Figure 2. No new matter has been added by way of these amendments.

The Rejection of the Claims Under 35 U.S.C. §112, First Paragraph, Should Be Withdrawn

Enablement

Claims 1-37 were rejected under 35 U.S.C. §112, first paragraph, for lack of enablement. While the Examiner acknowledges that the specification is enabled for a vaccine comprising SEQ ID NO:3 or 1 against Streptococcus pneumoniae Serotype 6B, the Examiner concludes that

the specification is not enabled for a vaccine for treating all pneumococcal infections comprising a variant of SEQ ID NO: 4 or 40 having at least one to 15 amino acid substitutions. This rejection is respectfully traversed.

The Examiner asserts that the data provided in the specification does not demonstrate that a polypeptide comprising SEQ ID NO:4, 40 or a variant thereof recited in claims 1-30 and 32-37 is capable of being used as a vaccine against pneumococcal infections. Applicants respectfully disagree.

The specification provides the following data:

1. Immune sera against SEQ ID NO:1 (R2; derived from Streptococcus pneumoniae serotype 4) provided passive immunization in mice challenged with Streptococcus pneumoniae serotype 6B. 80% of the mice immunized with rabbit immune serum raised against SEQ ID NO:1 survived the challenge. See, Example 3.

2. SEQ ID NO:3 (R1, derived from Streptococcus pneumoniae serotype 4) provided active immunization mice challenged with Streptococcus pneumoniae serotype 6B. 80% of the mice immunized with SEQ ID NO:3 survived the challenge. See, Example 3.

As illustrated in Figure 2 of the specification and in Appendix 1, the N-terminal choline binding proteins comprises two alpha helical domains referred to as Domain A and Domain C. As outlined above, the specification provides data demonstrating that SEQ ID NO:3 (referred to as R1) and SEQ ID NO: 1 (referred to as R2) provide protection against serotype R6X. With regard to the recitation of SEQ ID NO:4 and 40, the Examiner is respectfully requested to consider that the data in the instant specification demonstrates that SEQ ID NO:3 provides a cross-protective immune response to the bacterial serotype R6X. This cross protective effect is significant. In fact, Domain A of the R6X isolate (SEQ ID NO:9) and Domain A of the serotype 4 (SEQ ID NO:3) share only 55% identity (see Appendix 2), *yet a protective effect on the R6X serotype was produced upon administration of Domain A from serotype 4*. The claims of the

present invention recite SEQ ID NO:4 and 40. As both SEQ ID NO:4 and 40 possess a significantly higher degree of structural similarity to SEQ ID NO:3 than that of SEQ ID NO:9, one of skill in the art would conclude that the success of SEQ ID NO:3 for cross protecting against the R6x serotype renders probable the ability of SEQ ID NO: 4 and 40 (as claimed by the present invention) to also produce a protective effect.

To illustrate this point, the Examiner's attention is drawn to Appendix 3 which demonstrates that SEQ ID NOS:3 and 4 share significant structural similarity. In fact, the alpha helical domain A of serotype 4 (aa 137-242 of SEQ ID NO:3) and the alpha helical domain C of serotype 4 (aa 1-106 of SEQ ID NO:4) are *96.2% similar* and 82.1% identical. Similarly, Appendix 4 which demonstrates that SEQ ID NOS:3 and 40 share significant structural similarity. In fact, the alpha helical domain A of serotype 4 (aa 137-242 of SEQ ID NO:3) and the alpha helical domain C of serotype 4 (aa 279-409 of SEQ ID NO:40) are *94.4% similar* and 80.4% identical.

Moreover, SEQ ID NOS: 4 and 40 share an even greater sequence identity to the alpha helical domain of domain C of serotype R6x than SEQ ID NO:1. In fact, SEQ ID NO:4 shares 89.6% identity to the alpha helical domain C of serotype R6X (SEQ ID NO:10) (Appendix 5), while the alpha helical domain of SEQ ID NO:3 (R1) possesses only 81.1% sequence identity to SEQ ID NO:10. Similarly, the alpha helical domain C of SEQ ID NO:40 shares 86.9% identity to the alpha helical domain C of serotype R6x (SEQ ID NO:1). See, Appendix 6. Thus, both SEQ ID NO:4 and 40 share greater sequence identity to the alpha helical domain of the R6x serotype than that of R1 (SEQ ID NO:3) and thus one of skill would predict that SEQ ID NO:4 and 40 would be capable of providing the desired immune response. The importance of sequence conservation is further support by Bogaert *et al.* (2004) *Vaccine* 22:2209-220 (cited by the Examiner in the 10/11/06 Office Action). In discussing PspC based vaccines Bogaert *et al.* conclude that "Importantly, these proteins [PspC] appear to be highly conserved among pneumoccal strains, implicating a potential broad [immunogenic] coverage" (page 2215, column 2, lines 9-11). Thus, In view of the data in the specification, the structural relationship between SEQ ID NO: 3, 4, 10 and 40, and the state of art, claims 1-30 and 32-37 are enabled.

The Examiner further asserts on page 4, lines 12-17 of the October 11, 2006 Office Action that there are no experimental examples that teach protection against all pneumococcal

infections in a subject. The Examiner asserts "that pneumococcal infections encompass pneumonia, meningitis, otits media, sinusitis, bronchitis, empyema, spepsis, septicaemia, peritonitis, and arthritis" and cites Bogaert *et al.* (2004) *Lancet Infect. Dis.* 4:144-154 in support of this reasoning. However, pneumonia, meningitis, otits media, sinusitis, bronchitis, empyema, spepsis, septicaemia, peritonitis, and arthritis are all various diseases that are caused by pneumococcal infections. An effective vaccine against the pnueumoniae pathogen would prevent the progression of the recited disease states. See, for example, lines 1-3 of the abstract and lines 1-4 of paragraph 2, page 144 of Bogaert *et al.*

The Examiner further asserts that the specification does not support the broad claim scope because 1) the general tolerance to modification to the polypeptide and the extent of tolerance is not disclosed; 2) specific positions which can be predictably modified are not disclosed; and, 3) there is essentially no guidance as to which of the possible choices are likely to be successful. First, in order to satisfy the enablement requirement, the Applicant need not teach each amino acid substitution or deletion that may be made to produce a functional variant, such that no experimentation would be required to identify such variants. According to the applicable case law, the test of enablement is not whether experimentation is necessary to make and use an invention, but rather if experimentation is necessary, whether it is undue. *In re Angstadt*, 198 USPQ 214, 219 (C.C.P.A. 1976). The test of whether an invention requires undue experimentation is not based on a single factor, but rather a conclusion reached by weighing many factors. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

Factors to be considered in determining whether undue experimentation is required include the quantity of experimentation necessary, the amount of guidance provided in the specification, the presence of working examples of the invention in the application, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability in the art, and the breadth of the claimed invention. 8 USPQ2d at 1404. Accordingly, the holding of *Wands* does not require that an applicant identify every functional variant as argued by the Examiner. Rather, *Wands* sets out factors to be considered in determining whether undue experimentation is required to make and use the claimed functional variants.

The specification provides guidance for determining the regions of the alpha helical C-domain that would tolerate modification. See, for example, Figure 2 which provides a protein

alignment of 12 different CbpA polypeptides from different serotypes and further provides a consensus sequence (SEQ ID NO:40) of the CbpA protein. In addition, the specification provides clear support for the highly conserved domains in the alpha helical C-domain. See, for example page 37, lines 20-30 which specifies conserved domains that should be considered when making a vaccine. In addition, page 13, lines 5-31 and page 14, lines 1-12 provide exemplary substitutions that can be made to the CbpA protein in view of the extensive sequence alignment data provided in Figure 2. The specification also provides guidance for producing sequences having conservative substitutions (see, for example, page 26, lines 21-31 and page 27, lines 1-19) and assays for testing the immunogenic properties of the variants. See, for example, Examples 3 and 4 of the specification. Based on the teachings regarding the conserved domains of both SEQ ID NO:4 and SEQ ID NO:40 provided in the specification and known in the art, a skilled artisan could produce variants and test these modified variants to determine if they retain functional and/or immunogenic activity without undue experimentation. Making and testing such variants is routine to those of skill in the art.

In fact, it is now customary in the art to make and assay a number of sequences for a desired function in order to achieve the best results. For example, common techniques involve what is often referred to as "shuffling," as described for example in WO 9735966 published October 2, 1997 with inventors Minshull and Stemmer and entitled, "Methods and Compositions for Metabolic and Cellular Engineering." In short, as illustrated by work described in WO 9735966, one of skill in the art would be able to produce novel sequences and evaluate whether they met the limitations of the claims, as taught in the specification. One of skill in the art would then be able to identify whether those sequences retained the ability to treat or prevent pneumococcal infection as taught in the specification. With "shuffling" techniques, it is common to mutagenize individual sequences or a set of sequences which are then assayed for a desired activity. Such techniques may even make use of a library of sequences which is recursively mutagenized, screened for function using a functional assay, and re-mutagenized in order to find a sequence exhibiting optimal function. A copy of this publication is provided herewith as Appendix 7.

Such shuffling experiments are designed and are intended to encompass the generation and testing of a very large number of variant sequences for a desired function. As indicated by

these and other publications in the art, this level of experimentation is now considered routine in the art and thus would not be considered "undue experimentation" under *In re Wands,* 858 F.2d 731, 8 USPQ2d 1400 (Fed Cir 1988) and *In re Jackson*, 217 USPQ 804, 807 (Bd. Pat. App. & Int. 1982) (holding that a considerable amount of experimentation is permitted to practice the invention and is not undue if it is merely routine in the art or if the specification provides a reasonable amount of guidance and direction to perform such experimentation).

In support of the enablement rejection, the Examiner cites a number of references demonstrating the loss of function of a variety of proteins with amino acid substitutions (October 11, 2006 Office Action, page 6-8). References cited by the Examiner which relate to the enablement of the instant claims are discussed below.

1. With respect to Burgess *et al.*(1990) *The Journal of Cell Biology*, Applicants note that the lysine modified by the authors was known to be conserved between all members of the heparin-binding growth factors characterized at the time, including the acidic fibroblast growth factor modified by the authors. Again, one of skill in the art, when designing functional protein variants, would not target highly conserved domains without the expectation that *some* of the variants may not have function.

2. Lazar *et al.* (1988) *Mol. Cell Biol.* 8:1247-1252 describes transforming growth factor α (TGF-α), which is a mammalian polypeptide of 50 amino acids. The modifications described by Lazar include two amino acids of TGF-α which were known to be conserved among the family of EGF-like polypeptides. It would come as little surprise to one skilled in the art that the modification of such a conserved amino acid should lead to the loss of function described by the authors. One of the changes at position 47 described by the authors indicates that [Asn-47]- TGF-α retains biological activity. The authors note that interestingly, two of the EGF-like viral proteins, myxomal growth factor and Shope fibroma growth factor, have Asn instead of Asp in position 47. Thus, the reference supports Applicants' position that protein domains are important and that by aligning sequences, one of skill in the art can determine what sites would likely tolerate changes.

3. The Examiner cites Bowie *et al.* (1990) *Science* 247:1306-10 in support of the rejection for lack of an enabling disclosure. Bowie *et al.* is directed to the difficulties of predicting protein structure from primary sequence. The present application is not directed to methods of predicting protein structure, and the claims are not limited to a polypeptide having a particular 3-dimensional structure. Furthermore, Bowie *et al.* report that "[s]tudies . . . have revealed that proteins are surprisingly tolerant of amino acid substitutions . . . [f]or example, in studying the effects of approximately 1500 single amino acid substitutions at 142 positions in *lac* repressor, Miller and co-workers found that about one-half of all substitutions were phenotypically silent." Bowie *et al.* page 1306, column 2. Thus, according to the teachings of Bowie *et al.*, many of the variants of CbpA that meet structural limitations recited in the claims will also retain functional and/or immunogenic activity. When this statement is considered, the reference does not support a *prima facie* case of lack of enablement.

4. Kumar *et al.* (1989) *PNAS* 87: 1337-1341 teaches making alterations in amino acids 1-9 of the 9mer N-terminal epitope of MBP. The reference is silent as to the effect of the alterations at any position other than amino acid residue 4. In this position, the activity of the protein did change when the amino acid residue was altered. However, again, one of skill would not be surprised that an epitope of MBP when altered would modify function. Thus, once again, the reference supports Applicants' position that protein domains are important and that by aligning sequences, one of skill in the art can determine what sites would likely tolerate changes.

Accordingly, when all of the *Wands* factors are considered together, it is clear that the level of experimentation required to produce a vaccine comprising the recited variants of SEQ ID NO: 4 and 40 would not be undue in view of the state of the prior art, the relative skill of those in the art (to whom the making and testing of variants is routine), the predictability in the art, the amount of direction provided in the specification (which provides guidance regarding preferred types of amino acid substitutions and describes assays for identifying functional and/or

immunogenic variants), the breadth of the claimed invention (for which the scope is defined by structural limitations). These factors all favor a conclusion that one of skill in the art could practice the claimed invention without undue experimentation.

In view of the evidence and argument provided above, claims 1-30 and 31-37 satisfy the enablement requirement of 35 U.S.C. §112, and the Examiner is respectfully requested to withdraw the rejection.

Written Description

Claims 1-37 were rejected under 35 U.S.C. §112, first paragraph, for lack of written description. Specifically, the Examiner asserts that the specification has not disclosed the structure of the polypeptide recited in the pending claims genus and would not clearly apprise one of skill in the art that the inventors had possession of the claimed genus and all of the species encompassed thereby. This rejection is respectfully traversed.

Claims 1-30 and 32-37 are drawn to vaccines comprising a variant of SEQ ID NO:4 or 40 having at least one to 15 amino acid substitutions, wherein the polypeptide does not bind choline and the polypeptide protects against pneumococcal infection. Further dependant claims 8, 23 and 24 recite specific conserved amino acids as set forth in the CbpA consensus sequence of SEQ ID NO: 40; claims 3, 10, 18, 26 and 33 provide further functional/structural limitations that recite the polypeptide is identical to a polypeptide that is a competitive inhibitor of bacterial adhesion of pneumococcal and claim 4, 11, 19, 27, and 34 provides a further structural/functional limitation that recites that the polypeptide is identical to an N-terminal choline binding protein. The Examiner asserts that the specification fails to teach the critical protein residues required for a vaccine for a variant of SEQ ID NO:4 or 40, such that the skilled artisan is provided no guidance to test, screen or make the variants of SEQ ID NOS:4 or 40.

First, every species (e.g., "variant" of SEQ ID NOS:4 or 40) encompassed by the claimed invention need not be disclosed in the specification to satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. *Utter v. Hiraga*, 845 F.2d 993, 6 USPQ2d 1709 (Fed. Cir. 1988). The Federal Circuit has made it clear that sufficient written description requires simply the knowledge and level of skill in the art to permit one of skill to immediately envision the product claimed from the disclosure. *Purdue Pharm L.P. v. Faulding In.*, 230 F.3d 1320 1323,

596 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("One skilled in the art must immediately discern the limitations at issue in the claims.").

The description of a claimed genus can be by structure, formula, chemical name, or physical properties. *See Ex parte Maizel*, 27 USPQ2d 1662, 1669 (B.P.A.I. 1992), citing *Amgen v. Chugai*, 927 F.2d 1200, 1206 (Fed. Cir. 1991). A genus of DNAs may therefore be described by means of a recitation of a representative number of DNAs, defined by nucleotide sequence, falling within the scope of the genus, *or* by means of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997); *see also* Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, first paragraph, "Written Description" Requirement, 66 Fed. Reg. 1099, 1106 (2000). The recitation of a polypeptide wherein one or more amino acids is substituted by a *conserved* amino acid is sufficient to satisfy the written description requirement. An Applicant, however, may also rely upon functional characteristics in the description, provided there is a correlation between the function and structure of the claimed invention. *Id.*, *citing Lilly* at 1568.

The claims of the instant invention satisfy this requirement. Claims 1-30 and 32-37 recite vaccines comprising variants of SEQ ID NO:4 or 40 wherein the polypeptide comprises one to 15 amino acid substitutions. The specification provides an extensive description for amino acid substitutions. See, for example, page 26, lines 21-31 and page 27, lines 1-19) and provides known conserved domains (see, for example, Figure 2 which provides a protein alignment of 12 different CbpA polypeptides from different serotypes and further provides a consensus sequence (SEQ ID NO:40) of the CbpA protein; page 37, lines 20-30 which specifies conserved domains that should be considered when making a vaccine; and, page 13, lines 5-31 and page 14, lines 1-12 which provide exemplary substitutions that can be made to the CbpA protein in view of the extensive sequence alignment data provided in Figure 2. Thus, the specification provide *very specific and defined structural parameters* of the sequences encompassed by the claimed invention. Applicant submits that the knowledge and level of skill in the art would allow a person of ordinary skill to envision the claimed invention. Moreover, the claims further *recite functional characteristics* of the claimed genus. Specifically, claims 1-30 and 32-37 recite that the claimed sequences further retain the ability to treat or protect against pneumococcal

infection; thereby providing a functional characterization of the sequences claimed in the genus. Assays for determining such function can be found, for example, in Example 3 and 4 of the specification.

Consequently, contrary to the Examiner's conclusion, the sequences encompassed by claims 1-30 and 32-37 are defined by relevant identifying physical and chemical properties, thereby allowing the skilled artisan to envision the structure of the polypeptides of the invention for use. In summary, the description of a representative number of species *does not* require the description to be of such specificity that it would provide individual support for each species that the genus embraces. Applicants submit that the relevant identifying physical and chemical properties of the disclosed genus would be clearly envisioned by one of skill in the art and consequently, the Applicant was in possession of the necessary common attributes or features of the elements possessed by the members of the genus. Accordingly, the rejection of claims 1-30 and 31-37 under 35 U.S.C. §112, first paragraph, for lack of written description should be withdrawn.

In view of the above arguments, all grounds for rejection of claims 1-30 and 31-37 under 35 U.S.C. § 112, first paragraph have been overcome. Withdrawal of the rejection is respectfully requested.

Consideration Of Previously Submitted Information Disclosure Statement

It is noted that the initialed copy of the PTO Form 1449 that was submitted with Applicants' Information Disclosure Statement filed January 5, 2004 has not been completely signed off by the Examiner. As the Examiner has indicated that the file of the pending divisional application at the PTO no longer contains copies of citations 16-32, copies of these references are provided herewith. Accordingly, it is requested that an initialed copy of the Form 1449 be forwarded to the undersigned with the next communication from the PTO.

CONCLUSIONS

It is believed that all the rejections have been obviated or overcome and the claims are in condition for allowance. Early notice to this effect is solicited. If, in the opinion of the

Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned agent.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

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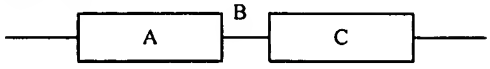
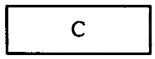
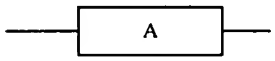
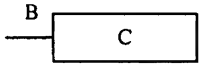
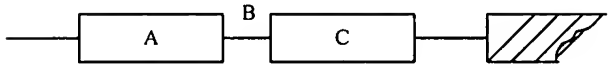
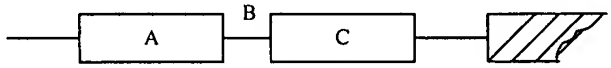
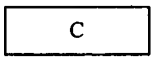
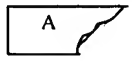
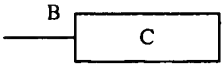
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to: Mail Stop Amendment, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

Pamela Lockley

LEGAL02/30152781v1

Appendix 1
Application No. 10/751,702
Reply to Office Action of October 11, 2006

SEQ ID NO	Serotype	Domains	Length
1	4		406
4	4		106
3	4		284
5	4		109
22	4		121
24	4		428
7	6		376
9	6		254
10	6		106
11	6		107
23	6		122

Appendix 2
Application No. 10/751,702
Reply to Office Action of October 11, 2006

Align Sequence Comparison of SEQ ID NO:3 and SEQ ID NO:9.

```
SEQ ID NO:3      1 ENEGATQVPTSSNRANESQAEQGEQPKKLDSERDKARKE-VEEYVKKIVG     49
                   ||||:||..||||.|.              :|..||.|: |:||::|::.
SEQ ID NO:9      1 ENEGSTQAATSSNMAK--------------TEHRKAAKQVVDEYIEKMLR     36

SEQ ID NO:3     50 ESYAKSTKKRHTITVALVNELNNIKNEYLNK--IVESTSESQLQILMMES     97
                   |  .:..:::||..|||..:|:.||.:||.:  ::|..|:.:|.   .|.
SEQ ID NO:9     37 E--IQLDRRKHTQNVALNIKLSAIKTKYLRELNVLEEKSKDELP---SEI     81

SEQ ID NO:3     98 RSKVDEAVSKFEKDSSSSSSSDSSTKPEASDTAKPNKPTEPGEKVAEAKK    147
                   ::|:|.|..||:||:                        .:||||||||||
SEQ ID NO:9     82 KAKLDAAFEKFKKDT----------------------LKPGEKVAEAKK    108

SEQ ID NO:3    148 KVEEAEKKAKDQKEEDRRNYPTITYKTLELEIAESDVEVKKAELELVKVK    197
                   |||||:|||:||||||||||||.||||||||||.||:||:|||||||.:
SEQ ID NO:9    109 KVEEAKKKAEDQKEEDRRNYPTNTYKTLELEIAEFDVKVKEAELELVKEE    158

SEQ ID NO:3    198 ANEPRDEQKIKQAEAEVESKQAEATRLKKIKTDREEAEEEAKRRADAK--    245
                   |.|.|:|..||||:.:||||:||||||:.||||||:|||||||:||||
SEQ ID NO:9    159 AKESRNEGTIKQAKEKVESKKAEATRLENIKTDRKKAEEEAKRKADAKLK    208

SEQ ID NO:3     246 -------EQGKPKGRAKRGVPGELATPDKKENDAKSSDSSVGEETL    284
                          :||||||||||||||||||||||||||||||||||||
SEQ ID NO:9     209 EANVATSDQGKPKGRAKRGVPGELATPDKKENDAKSSDSSVGEETL    254
```

* Alignment was run using the Align software: Program: needle; Matrix: EBLOSUM62; Gap_penalty: 10.0; Extend_penalty: 0.5

Appendix 3
Application No. 10/751,702
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Align Sequence Comparison of SEQ ID NO:3 and SEQ ID NO:4.

```
SEQ ID NO:3       1 ENEGATQVPTSSNRANESQAEQGEQPKKLDSERDKARKEVEEYVKKIVGE     50

SEQ ID NO:4       1                                                        0

SEQ ID NO:3      51 SYAKSTKKRHTITVALVNELNNIKNEYLNKIVESTSESQLQILMMESRSK    100

SEQ ID NO:4       1                                                        0

SEQ ID NO:3     101 VDEAVSKFEKDSSSSSSSDSSTKPEASDTAKPNKPTEPGEKVAEAKKKVE    150
                                                    :|.:|||||:||||
SEQ ID NO:4       1                                 KPEKKVAEAEKKVE     14

SEQ ID NO:3     151 EAEKKAKDQKEEDRRNYPTITYKTLELEIAESDVEVKKAELELVKVKANE    200
                    ||:|||:||||||||||||.||||||||||||||||||||||.:|.|
SEQ ID NO:4      15 EAKKKAEDQKEEDRRNYPTNTYKTLELEIAESDVEVKKAELELVKEEAKE     64

SEQ ID NO:3     201 PRDEQKIKQAEAEVESKQAEATRLKKIKTDREEAEEEAKRRADAKEQGKP    250
                    ||:|:|:|||:||||||:||||||:||||||::||||||:|
SEQ ID NO:4      65 PRNEEKVKQAKAEVESKKAEATRLEKIKTDRKKAEEEAKRKA             106

SEQ ID NO:3      251 KGRAKRGVPGELATPDKKENDAKSSDSSVGEETL    284

SEQ ID NO:4      107                                     106
```

*Amino Acids 137-242 of SEQ ID NO:3 share 96.2% similarity to SEQ IDNO:4.
** Alignment was run using the Align software: Program: needle; Matrix: EBLOSUM62; Gap_penalty: 10.0; Extend_penalty: 0.5

Appendix 4
Application No. 10/751,702
Reply to Office Action of October 11, 2006

Align Sequence Comparison of SEQ ID NO:3 and SEQ ID NO:40.

```
SEQ ID NO:3       1 EPGEKVAEAKKKVEEAEKKAKDQKEEDRRNYPTITYKTLELEIAESDVEV     50
                    :|.:||||||:||||||:|||:||||||||||||.||||||||||||||||
SEQ ID NO: 40 297 KPEKKVAEAEKKVEEAKKKAEDQKEEDRRNYPTNTYKTLELEIAESDVEV     347

SEQ ID NO:3      51 KKAELELVKVKANEPRDEQKIKQAEAEVESKQAEATRLKKIKTDREEAEE    100
                    |||||||||.:|.|.|:|:|:|||:||||||:||||||:||||||::|||
SEQ ID NO: 40 348 KKAELELVKEEAKESRNEEKVKQAKAEVESKKAEATRLEKIKTDRKKAEE    398

SEQ ID NO:3     101 EAKRRA      106
                    ||||:|
SEQ DI NO:4     399 EAKRKAA     409
```

*Amino Acids 137-242 of SEQ ID NO:3 share 94.4% similarity to SEQ IDNO:40.
** Alignment was run using the Align software: Program: needle; Matrix: EBLOSUM62; Gap_penalty: 10.0; Extend_penalty: 0.5

Appendix 5
Application No. 10/751,702
Reply to Office Action of October 11, 2006

Align Sequence Comparison of SEQ ID NO:4 and SEQ ID NO:10.

```
SEQ ID NO:4       1 KPEKKVAEAEKKVEEAKKKAEDQKEEDRRNYPTNTYKTLELEIAESDVEV      50
                    |..|||||||||||||:|||:||||||||||||||||||:||||||||:|
SEQ ID NO: 10     1 KSGKKVAEAEKKVEEAEKKAKDQKEEDRRNYPTNTYKTLDLEIAESDVKV      50

SEQ ID NO:4      51 KKAELELVKEEAKEPRNEEKVKQAKAEVESKKAEATRLEKIKTDRKKAEE     100
                    |:|||||||||||||||:|||:||||||:||||||||||||.||||||||||
SEQ ID NO:10     51 KEAELELVKEEAKEPRDEEKIKQAKAKVESKKAEATRLENIKTDRKKAEE     100

SEQ ID NO:4     101 EAKRKA     106
                    ||||||
SEQ ID NO:10    101 EAKRKA     106
```

* SEQ ID NO:4 shares 97.2 % similarity to SEQ IDNO:10.
** Alignment was run using the Align software: Program: needle; Matrix: EBLOSUM62; Gap_penalty: 10.0; Extend_penalty: 0.5

Appendix 6
Application No. 10/751,702
Reply to Office Action of October 11, 2006

Align Sequence Comparison of SEQ ID NO:40 and SEQ ID NO:10

```
SEQ ID NO: 40     1  PEKKVAEAEKKVEEAKKKAEDQKEEDRRNYPTNTYKTLELEIAESDVEV     49
                     ..|||||||||||||:|||:||||||||||||||||||:|||||||||:|
SEQ ID NO:10      1 KSGKKVAEAEKKVEEAEKKAKDQKEEDRRNYPTNTYKTLDLEIAESDVKV     50

SEQ ID NO: 40    50 KKAELELVKEEAKESRNEEKVKQAKAEVESKKAEATRLEKIKTDRKKAEE     99
                    |:|||||||||||||.|:|||:|||||:||||||||||||.||||||||||
SEQ ID NO: 10    51 KEAELELVKEEAKEPRDEEKIKQAKAKVESKKAEATRLENIKTDRKKAEE    100

SEQ ID NO: 40   100 EAKRKAA    106
                    ||||||
SEQ ID NO: 10   101 EAKRKA     106
```

* Amino acids ??-?? of SEQ ID NO:40 shares 94.4 % similarity to SEQ IDNO:10.
** Alignment was run using the Align software: Program: needle; Matrix: EBLOSUM62; Gap_penalty: 10.0; Extend_penalty: 0.5